REMARKS

Applicants respectfully request reconsideration of the present application in view of the amendment to pending Claims 21, 24, 26, 30, and 36-39 and the foregoing reasons.

Pending Claims

Upon entry of the amendment, Claims 21, 24, 26, 30, and 36-39 will be pending, with Claims 1-20, 22-23, 25, 27-29, and 31-35 having been previously cancelled.

The Amendments

Pending Claims 21, 24, 26, 30, and 36-39 have been amended to emphasize the role of the benzazole compounds in the pharmaceutical compositions, which are vaccine compositions wherein the benzazole compounds act as adjuvants to stimulate an immune response to the antigen. Support for the amendment is found throughout the specification, particularly in paragraphs [0018] and [0025], and in the paragraph after [00214] at the bottom of page 84 of the application as filed. Entry of the amendment is respectfully requested.

Claim Objections

Applicants note with appreciation the Office's acknowledgement of the allowability of Claim 30 reciting compositions comprising certain benzimidazole compounds if the claim was rewritten in independent form to include the limitations of Claim 21 from which it depends. In view of the amendment to Claim 21, Claim 30 has been maintained in its current dependent form, as Applicants will address the objection to Claim 21 below.

The 35 U.S.C. §103 rejection

Claims 21, 24, 26, and 36-39 are rejected under 35 U.S.C. §103(a) as being obvious over Das *et al.* (US Patent 6,596,746) in view of Klaviniskis *et al.* (US Application No. 2003/0147923) and Ryan (US Patent 4,171,353). Applicants note that Claim 21 has now been amended, and the remaining pending claims all depend directly or indirectly from Claim 21. Applicants respectfully traverse the rejection and its supporting remarks for the following reasons.

The Supreme Court in KSR International Co. v. Teleflex Inc., 127 S.Ct. 1727 (2007) recently reviewed the analysis for determining if an invention is obvious over the teachings of the prior art and affirmed the factual analysis set forth in Graham v. John Deere Co. of Kansas City, 383 U.S. 1, 17-18 (1966) Id. at 1734. The factual inquiries necessary in an analysis of obviousness by the Office is delineated in MPEP 2141:

A) Determining the scope and contents of the prior art;

(B) Ascertaining the differences between the prior art and the claims in issue;

(C) Resolving the level of ordinary skill in the pertinent art; and

(D) Evaluating evidence of secondary considerations

MPEP 2141 further states that:

When applying 35 U.S.C. 103, ...

(A) The claimed invention must be considered as a whole;

(B) The references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination;

(C) The references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention; and

(D) Reasonable expectation of success is the standard with which obviousness is determined.

This teaching, suggestion, motivation test for obviousness was also addressed by the Supreme Court in KSR, which confirmed that when such a test is applied with flexibility and in a non-mandatory manner, "[t]here is no inconsistency between the idea underlying the [teaching, suggestion, motivation] test and the Graham analysis".

After application of the facts of Applicants' invention in the context of the Graham analysis and consistent with the ruling in KSR, it will be shown that Applicants' claimed invention meets the criteria of 35 U.S.C. § 103.

The Scope and Content of the Prior Art

The Scope and Content of Das et al .US 6,596,746

Das *et al.* discloses certain cyclic compounds and their use for inhibiting tyrosine kinases for treating oncological and autoimmune diseases mediated by these kinases. Das *et al.* does not disclose or teach the compounds in a vaccine composition. Not surprisingly, Das *et al.* also does not disclose or teach pharmaceutical compositions containing the compounds with antigens, a key vaccine component. Das *et al.* does not disclose any evidence of the compounds as having suitable immunological properties that would suggests their use as an adjuvant in a vaccine to stimulate an immune response to an antigen.

The Scope and Content of Klaviniskis et al. US Application No. 2003/0147923

The discovery of the immunostimulatory properties of the spores of *Bacillius subtilis* is central to scope of the invention of Klaviniskis *et al.* Uses of the spores as taught by Klaviniskis (see [0079] The Invention Has the Following Applications) include a) stimulating the *in vitro* generation of dendritic cells, wherein the dendritic cells are then used as therapeutic agents to generate T cells *in vivo* b) administering the spores directly to tumor cells to generate T cells that can recognize cancer antigens within the tumor c) stimulating IL-12 in subjects to treat allergic reactions in combination with anti-allergenic agents, d) use of spores in cancer vaccines in combination with anti-cancer agent, e) use in vaccines to potentiate a response to the vaccine components, f) activating innate immunity, and g) boosting immunity in previously immunized patients. It should be noted however that Klavinikis *et al.* does not disclose or teach a *single vaccine composition* containing the adjuvant spores, an antigen, and a therapeutic agent. Furthermore, Klavinikis *et al.* does not disclose the compounds of the instant claims.

The Scope and Content of Ryan et al. US Patent 4,171,353

In the brief description of the prior art, Ryan describes known adjuvants as including oil-in-water type adjuvants that operate by slowly releasing the antigen from the oil emulsion, their advantages over the more common aluminum adjuvants, and their disadvantages resulting in their rare use in humans. Ryan then goes on to disclose the invention, which is use of choline

esters as adjuvants based on the surprising discovery of the previously unrecognized property of the choline esters to enhance an immune response of an animal to an antigen. Ryan however does not disclose vaccine compositions comprising a compound of the instant claims.

The Differences Between the Cited Art and the Claimed Invention

It is well established that in vaccine compositions, immune responses to antigens in the vaccines are more effectively raised when adjuvants are present during the administration of an antigen. Adjuvants recruit components of the innate immune system to the site of administration, thereby initiating the biological process wherein the immune system recognizes the antigen as a foreign object and mounts an appropriate response, including the development and establishment of lasting immunological cells of the adaptive immune system such as memory T cells and memory B cells. Such cells would be able to recognize infections by the disease causing agents that the antigens mimic, even long after the vaccination event.

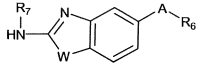
The present application discloses benzazole compounds that have been found to have the previously unknown property of stimulating components of the immune system. Method 2 on page 122 of the application as filed discloses that compounds 2-67 were found to increase production of TNF-α, a protein that plays a critical, early role in initiating the establishment of an adaptive immune system to mount a lasting defense to disease causing agents that resemble the antigens. Thus Claim 21 has now been amended to include the claim limitation of the benzazole compound adjuvants stimulating an immune response *to the antigen* to underscore the critical relationship between the benzazole and the antigen vis-à-vis the components of the immune system.

The disclosures of the present application, Klaviniskis *et al.*, and Ryan are similar to the extent that all three disclose novel uses of compounds or agents that were not previously known to have adjuvant properties. The adjuvants in the present application are benzazole compounds, those of Klaviniskis *et al.* are *Bacillius subtilis* spores, and those of Ryan are choline esters. All three applications teach use of the adjuvants in a vaccine compositions to stimulate an immune response to whatever antigen is present in the composition. These vaccines are also taught for

use in immunizing subjects against future infections. However, neither Klaviniskis *et al.* nor Ryan teach a vaccine composition comprising the benzazole compound of the instant claims.

The combination of references do not teach the claimed benzazole compound.

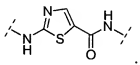
The Office acknowledges that in the combination of the three cited references, the claim limitation relating to the compounds is provided only by Das *et al.* and not by Klaviniskis *et al.* or Ryan. Turning thusly to Das *et al.*, Applicants submit that this reference does not teach or suggest the compounds of the instant claims, and therefore does not teach the claimed vaccine composition comprising the compounds. The compounds in the compositions of the instant claims possess a benzazole scaffold having a NH substituent substituted with a cyclic R_7 group, i.e.



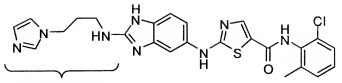
where R_7 is selected from the group consisting of carbocyclyl, unfused carbocyclylcarbocyclyl, substituted aryl, unsubstituted aryl, substituted heteroaryl, unsubstituted heteroaryl, substituted fused arylheteroaryl, unsubstituted fused arylheteroaryl, substituted unfused arylaryl and unsubstituted unfused arylaryl.

Applicants note that the R_6 group in the instant claims must also be a cyclic group.

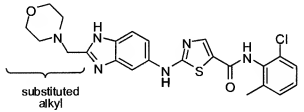
In contrast, Das *et al.* discloses 580 examples, all of which having the following common core structure:



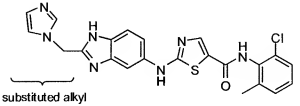
Of these 580 examples *only* three contain a benzazole group, namely the benzimidazoles of Example 572 (column 266, lines 5-14), Example 573 (column 266, lines 5-14), and Example 574 (column 266, lines 5-14):



Example 572:



Example 573:



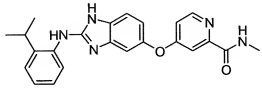
Example 574: substituted alkyl

Notably, none of these compounds possess a NH moiety substituted with a cyclic group where the NH moiety is attached directly to the five membered imidazole portion of the benzimidazole ring. In example 572, the substituent attached to the NH moiety is a substituted alkyl group. In examples 573 and 574, both compounds lack an NH moiety on the substituent attached to the imidazole portion of the benzimidazole ring.

The compounds of the instant claims are not isomers of those disclosed in Das et. al..

Applicants respectfully disagree with the Office's characterization (citing in re Jones and in re Norris) of the compounds of the instant claims as being isomers of the compounds of Das *et al.*. Isomeric compounds are compounds that have the same analytical composition of atoms but differ in their arrangement. As shown *supra*, none of the instantly claimed compounds are isomers of the compounds as disclosed in Das *et al.* since the instantly claimed substituents are structurally different from those of Das *et al.* One of the skill in the art would not construe the substituents highlighted in Examples 572, 573, and 574 in Das *et al.* as being an isomer of a (cyclic)NH- moiety as exemplified by the compounds in Claim 30, which corresponds to

examples 2, 3, 4, 5, 7, 8, 9, 10, and 11 in Table 1 of the present application. For example, Example 2 of Table 1 discloses



Further, the cited references neither by themselves nor in combination suggest or motivate one of ordinary skill in the art to modify the reference or to combine reference teachings to arrive at the compounds of the instant claims. From the 580 compounds disclosed in Das *et al.*, it is not obvious to a person of skill in the art to pick and choose the three benzimidazole compounds and then to modify them to obtain the instantly claimed compounds having a NH moiety substituted with a cyclic R_7 substituent, where the R_7NH moiety is directly attached to the benzimidazole ring.

Resolving the level of ordinary skill in the pertinent art

For the sake of argument, the level of skill in the art is assumed to be a person having a baccalaureate degree in the biological or chemical sciences.

Evaluating evidence of secondary considerations

Objective evidence of non-obviousness vaccine compositions comprising the claimed compounds can be found in Method 2 on page 122 of the application as previously discussed, where compounds 2-67 were surprisingly found to increase production of TNF-α, thereby providing support for their use as adjuvants to stimulate an immune response to an antigen.

The Combined Teachings Do Not Teach or Suggest the Claimed Vaccine Compositions

After the teachings of the cited art are compared to the claims, the combined teachings are evaluated to determine the desirability of the combination and whether doing so yields no more than a predictable result. See KSR, supra at 1740.

Since Das *et al.* does not disclose the vaccine compositions of the instant claims, the Office has combined Das with the adjuvants and antigens taught by Klaviniskis *et al.* or Ryan. Applicants submit that when the references are viewed as a whole however, the compounds of Das *et al.* would not be added to such a vaccine composition to arrive at the instant claims for the following reasons:

1. Das *et al.* does not teach the benzazole compounds.

As discussed above, the compounds disclosed by Das *et al.* are not the compounds of the instant claims. Further, Das does not provide any motivation or suggestion to choose the three benzimidazole compounds from the 580 compounds disclosed and modify those compounds to arrive at the compounds in the claimed pharmaceutical vaccine compositions. Without such motivation or suggestion, a *prima facie* case of obviousness cannot be established based solely on structural similarity (Takeda Chem. Indus., Ltd. v. Alphapharm Pty. Ltd. Fed. Cir. June 28, 2007).

2. There is no teaching that the compounds disclosed by Das *et al* have adjuvant properties.

As was previously mentioned, adjuvants play an important role in ensuring the effectiveness of a vaccine by stimulating an immune response in a subject to the antigen in the vaccine. Thus adjuvants are distinct from agents that merely stimulate the immune system as the immune response to the antigen is the desired outcome of an effective vaccine. Absent any teaching that the compounds of Das *et al.* are capable of acting as adjuvants, there is no motivation to combine those compounds with an antigen, as such compounds would not be expected to stimulate an immune response to the antigen.

3. Das *et al*, Klaviniskis *et al*, and Ryan, alone or in combination, do not teach co-formulations of a therapeutic agent composition with a vaccine formulation to form the claimed vaccine formulation.

The Office asserts that vaccines and therapeutic agents can be combined in a single pharmaceutical composition simply because they are separately taught to be used to treat a common disease. The instant claims are directed to pharmaceutical vaccine compositions. Das

et al does not teach co-formulations of its compound formulations with a vaccine formulation. Since there is no teachings or suggestions that the vaccine formulations taught by Klaviniskis *et al.* or Ryan include (non-vaccine) therapeutic agents, combining Das *et al.* with Klaviniskis *et al.* or Ryan does not cure this deficiency.

4. The State of the Art does not provide vaccine compositions that also include a therapeutic agent.

Fundamentally, therapeutic agents are generally not combined with vaccine components to arrive at a combination vaccine/therapeutic agent composition, and the Applicants are not aware of any such vaccine compositions that currently exist in the art. A number of reasons exist for the lack of this combination. First, vaccines typically have a very specific and limited dosing schedule (both in the frequency and amount of dosing) that is distinct from the dosing schedule of therapeutic agents. Secondly, vaccines are often administered prior to infections, whereas therapeutic agents, such as those of Das *et al.* would not be given prophylactically. Third, the mode of administration of vaccines are typically subcutaneous injections whereas most therapeutic agents are administered intravenously or orally. The teachings of Das *et al.* do not provide any reasons why there would be an advantage to having the compounds combined with a vaccine in a single composition, particularly in view of the convenience and advantages of treating a subject with these agents separately.

5. The teachings of Das *et al* do not provide for an expectation of success in combining the Das *et al* compounds, an adjuvant, and an antigen in a vaccine composition as is claimed.

The combination of the three references would place the adjuvants and antigens of Klaviniskis *et al.* or Ryan with the compounds of Das *et al.* However, the compounds of Das *et al.* are disclosed for use in inhibiting T cell activation through the inhibition of kinases such as Lck (see column 1 lines 61-67):

> Inhibitors of Lck are thus useful in the treatment of T-cell mediated disorders such as chronic diseases with an important T cell component, for example rheumatoid arthritis, multiple sclerosis and lupus, as well as acute diseases where T cells are

known to play an essential role, for example acute transplant rejection and delayed-type hypersensitivity (DTH) reactions.

With respect to uses in combination with other therapeutic agents, Das *et al.* discloses as exemplary compounds that are also inhibitors of components of the immune system:

> Exemplary such other therapeutic agents include the following: cyclosporins (e.g., cyclosporin A), CTLA4-Ig, antibodies such as anti-ICAM-3, anti-IL-2 receptor (Anti-Tac), anti-CD45RB, anti-CD2, anti-CD3 (OKT-3), anti-CD4, anti-CD80, anti-CD86, monoclonal antibody OKT3, agents blocking the interaction between CD40 and gp39, such as antibodies specific for CD40 and/or gp39 (i.e., CD154), fusion proteins constructed from CD40 and gp39 (CD40Ig and CD8gp39), inhibitors, such as nuclear translocation inhibitors, of Nf-kappa B function, such as deoxyspergualin (DSG), non-steroidal antiinflammatory drugs (NSAIDs) such as ibuprofen, steroids such as prednisone or dexamethasone, gold compounds, antiproliferative agents such as methotrexate, FK506 (tacrolimus, Prograf), mycophenolate mofetil, cytotoxic drugs such as azathiprine and cyclophosphamide, **TNFα inhibitors such as tenidap, anti-TNF antibodies or soluble TNF receptor such as etanercept (Enbrel)**, rapamycin (sirolimus or Rapamune), leflunimide (Arava), and cyclooxygenase-2 (COX-2) inhibitors such as celecoxib (Celebrex) and rofecoxib (Vioxx), or derivatives thereof ***(emphasis added)***.

While the compounds of the instant claims have been found to stimulate TNF-α production thereby providing evidence for their use as adjuvants in a pharmaceutical vaccine, the compounds of Das *et al.* in contrast are expected to inhibit the immune system and are taught as being used preferably in conjunction with similar inhibitors. Thus when taken as a whole, Das *et al.* teaches away from inclusion of its disclosed compounds in a single pharmaceutical vaccine composition along with an adjuvant spore/antigen composition of Klaviniskis *et al.* or choline ester/antigen composition of Ryan, as the ability of the spore or choline ester adjuvants to stimulate the immune system to respond to the antigen in the composition would be compromised by the presence of the Das *et al.* compounds.

For the reasons stated above, Applicants request that the Office withdraw the rejection under 35 U.S.C. §103(a).

Applicants believe that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

Respectfully submitted,

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